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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,061	03/05/2002	Francis Y.F. Lee	LD0268 NP	6706

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,061	LEE, FRANCIS Y.F.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005 and 18 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

This Office Action is in response to Applicant's amendment and response filed on March 28, 2005 and April 18, 2005 wherein claims 1 and 6 are cancelled and claims 101-112 have been amended and claims 113-130 are newly submitted.

Currently, claims 101-130 are pending in this application.

Claims 101-130 as amended now are examined on the merits herein.

Applicant's amendment wherein claim 101 has been amended, filed March 28, 2005 and April 18, 2005 with respect to the rejection made under 35 U.S.C. 112 first paragraph for lack of scope of enablement for treating any cancers of record stated in the Office Action dated November 17, 2004 has been fully considered and is found persuasive to overcome this rejection since the particular cancers have been recited. Therefore, the said rejection is withdrawn.

The following is the new ground(s) of rejection(s).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 101, 105-111, 113-116, and 126-130 are rejected under 35 U.S.C. 102(e) as being anticipated by Danishefsky et al. (US 6867305, PTO-892).

Danishefsky et al. discloses that administering a pharmaceutical composition comprising the instant particular compound (see the structure of the compound at col.108 lines 29-45) also known as C-15-Aza-EpoB (see Figure 33), azaepothilone b or ixabepilone to a mammal, is useful in methods of treating one or more of cancers such as cancerous solid tumors, refractory tumors, metastatic breast cancer, lung cancer, prostate cancer, and pancreatic cancer and methods for the treatment of cancer which has developed a muti-drug resistance (MDR) (see abstract, col. 59 lines 27-44).

In particular, the compounds of Danishefsky et al. such as the instant compound have been found effective not only reversing muti-drug resistance (MDR) in cancer cells both in vitro or in vivo, e.g., resistant to taxane treatment (paclitaxel or Taxol), but also more cytotoxic towards MDR cells than normal cells and as **synergistic** agents, which are more active in **combination** with other cytotoxic agents or anticancer agents than the individual drugs alone (see col.30 lines 15-32; col.59 line 45-59). Those other cytotoxic agents or anticancer agents such as 5-fluorouracil (5-FU) are used in combination with the instant compounds (see col.59 line 60 to col.60 line 7).

The combination compositions of the instant compound and the other cancer drug can be administered substantially and simultaneously (concurrently) to humans or animals orally (see col.59 line 45-59; col. 57 lines 8-10) in various dosage forms (col.56-57).

Note that Danishefsky et al. discloses that the effective amount of the instant compound to be administered is in the range of about 0.01 mg to 50 mg/kg/day or 1 mg to 25 mg/kg/day (see col.57 lines 20-24), which are same or overlapping with the effective amounts, indicated in Applicant's specification (see page 39-41 of the specification).

Thus, Danishefsky et al. anticipates Claims 101, 105-111, 113-116, and 126-130.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 102-104, 112, and 117-125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danishefsky et al. (US 6867305) in view of Miwa et al. European Journal of Cancer (1998), 34(8), 1274-1281, of record).

The same disclosure of Danishefsky et al. has been discussed in the 102(e) rejection set forth above (see supra at page 11-12).

Danishefsky et al. does not expressly disclose the employment of capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer.

Miwa et al. discloses that capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), which is finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors. See abstract and the entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ capecitabine in combination with the instant particular compound in a pharmaceutical composition and a method for treating cancer, since, first, 5-fluorouracil is known to be useful in combination with the instant particular compound in a pharmaceutical composition for methods for treating cancer effectively and **synergistically,** according to Danishefsky et al.

Second, capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), is known to be much safer and more effective than 5-FU and finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors.

Therefore, one of ordinary skill in the art would have reasonably expected that combining capecitabine in combination with the instant particular compound in a pharmaceutical composition for methods for treating cancer, would have been much safer and even more effective than the combination of 5-FU and the instant compound in treating the same.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 101-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. (WO 99/02514, of record) in view of The Merck Index, (12th ED), 1996, and Miwa et al. European Journal of Cancer (1998), 34(8), 1274-1281 essentially for same reasons of record stated in the Office Action dated November 17, 2004.

Vite et al. discloses that the instant particular compound (see Example 3 at page 48) is useful in treating various types of cancers or tumors including the cancers recited in the instant claims 105-110 (see page 8-10). More important, Vite et al. discloses that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment. See page 10.

The prior art does not expressly disclose the employment of the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer.

The Merck Index teaches that fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy, i.e., combing with other anti-cancer agents as cancer chemotherapy drug regimens (see MISC-10).

Miwa et al. discloses that capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), which is finally converted to 5-fluorouracil (5-FU) by dThdPase in

tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors. See abstract and the entire article.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the instant particular compound in combination with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer, since the instant particular compound is known to be useful in treating various types of cancers or tumors including the cancers herein and also useful in combination with known anti-cancer and cytotoxic agents for cancer treatment according to Vite et al.

Moreover, fluorouracil (5-FU) is well-known to be used in combination cancer chemotherapy according to The Merck Index. Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine), is known to be finally converted to 5-fluorouracil (5-FU) by dThdPase in tumors, and should be much safer and more effective than 5-FU, for treating cancers or various types of tumors according to Miwa et al.

Therefore, one of ordinary skill in the art would have reasonably expected that combining the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine and the instant compound, both known useful for the same purpose, i.e.,

treating cancers, would improve the therapeutic effects for treating the same, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Further, the teachings of Vite et al. that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment, and the combination cancer chemotherapy drug regimens in Merck Index, have clearly provided the motivation for the combination claimed herein.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments and Exhibit A filed March 28, 2005 and April 18, 2005 with respect to this rejection made under 35 U.S.C. 103(a) as being unpatentable over Vite et al. in view of The Merck Index, and Miwa et al. of record in the previous Office Action have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant primarily argues that "an impermissible picking and choosing to reconstruction the applicant's invention based on the instant disclosure". It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction

based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971). See MPEP 2145.

In this case, the teachings of Vite et al. that the instant compound is useful in combination with known anti-cancer and cytotoxic agents for cancer treatment, and the combination cancer chemotherapy drug regimens in Merck Index, have provided the motivation for the combination claimed herein.

It is also noted that "the rationale to modified or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or implied contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law." (emphasis added, see MPEP 2144, citing In re fine, 837 F.2d 1071, 5 USPQ 2d 1596 (Fed. Cir. 1988), for example). In this case, it has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Therefore, one of ordinary skill in the art would have reasonably expected that combining the specific anti-cancer agents such as fluorouracil (5-FU) and/or

capecitabine and the instant compound, both known useful for the same purpose, i.e., treating cancers, would improve the therapeutic effects for treating the same, and/or would produce additive therapeutic effects in treating the same.

Further, Applicant's assertion in the remarks that Exhibit A demonstrates the claimed combination of capecitabine and ixabepilone shows synergistic activity against human colon tumor xenogragts (see page 12-13 of Applicant's response) has been considered but is not found convincing since Exhibit A herein is unclear as to how the graphical presentation herein may be taken to demonstrate unexpected and synergistic effect in the instant invention. Applicant has the burden to explain the experimental evidence. See *In re Borkowski and Van Venrooy* 184 USPQ 29 (CCPA 1974).

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 101-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 12 of U.S. Patent No. 6,686,380.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent, i.e. claim 12, is drawn to the same cancer or tumor treatment method comprising administering the same compound as herein with a chemotherapeutic agent. In particular, the patent discloses that chemotherapeutic agents includes pyrimidine analogs (see col.11 line 66). 5-Fluorouracil and its prodrug capecitabine are known pyrimidine analogs (see Merck Index ,THER-13).

Thus, the instant claims 101-112 are seen to anticipate claim 12 of U.S. Patent No. 6,686,380.

Claims 101-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33-35 and 57-58 of U.S. Patent No. 6,605,599.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent, i.e. claims 33-34 and 57-58, are drawn to the same cancer or tumor treatment method comprising administering the same compound as herein with a chemotherapeutic agent. In particular, the patent discloses that chemotherapeutic agents includes pyrimidine analogs (see col.11 line 66). 5-Fluorouracil and its prodrug capecitabine are known pyrimidine analogs (see Merck Index ,THER-13).

Thus, the instant claims 101-112 are seen to anticipate claims 33-35 and 57-58 of U.S. Patent No. 6,605,599.

Applicant's same or substantially similar arguments as the 103(a) rejection with respect to obviousness-type double patenting rejections in the previous Office Action have been fully considered but are not deemed persuasive as discussed above.

Moreover, the patent particularly discloses that chemotherapeutic agents includes pyrimidine analogs (see for example, 6,605,599, col.11 line 66). 5-Fluorouracil and its prodrug capecitabine are known pyrimidine analogs (see Merck Index ,THER-13).

Therefore, said rejections are maintained.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner
Art Unit 1617
June 22, 2005